51. The antibody according to claim 36, which is produced using a partial peptide of said matrix metalloproteinase protein selected from the group consisting of SEQ ID NOS: 5, 6, 7 and 8.

52. The antibody according to claim 36, which is not crossreactive with any one of the matrix metalloproteinase (MMP) protein selected from the group consisting of MMP-1, MMP-2, MMP-3, MMP-7, MMP-8 and MMP-9.

53. The antibody according to claim 36, wherein said partial peptide or salt thereof comprises at least 8 continuous antigenic amino acid residues of SEQ ID No: 2 which are characteristic of said MMP protein.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

With regard to the Restriction Requirement, Applicants hereby again affirm the election of Group I, claims 14-22 and 26. It is noted that the election was made by the Applicants while retaining their right to file a Divisional Application directed to the non-elected subject matter with the protection afforded by 35 USC § 121.

Claims 30-35, directed to non-elected subject matter, remain in the application. It is again requested that they be permitted to remain in the dormant condition pending the filing of a

divisional application. Applicants note that claims 23-25, also directed to non-elected subject matter, have been rewritten as new claims 45-47 for possible rejoinder under *In re Ochiai* and *In re Brower*. Applicants request that these claims be examined upon the allowance of the elected claims.

With respect to Applicants' claim for domestic priority under 35 U.S.C. §120, Applicants note that the Examiner has failed to acknowledge such claim for priority in item 15 of the Office Action Summary. Applicants respectfully request such acknowledgment in the Examiner's next Official Action.

The specification has been amended to update the status of Parent Application Serial Number 09/000,041 filed February 20, 1998.

Claims 14-26 have been cancelled without prejudice and replace with new claims 36-53. New claims 36-48 have been added to direct to the claimed subject matter allowed in the parent application (Patent Application Serial Number 09/000,041, filed February 20, 1998, now U.S. Patent 6,191,255). Further, new claims 49-53 have been added to further protect specific embodiments of the present invention. Support for the new claims is readily apparent from the teachings of the specification and the previously presented claims. Specific support for new claims 49-53 can be found on page 31, lines 17-19, pages 32-38 and Example 3 of the specification.

With regard to the rejection of claims 14-22 and 26 under 35 U.S.C. § 112, second paragraph, Applicants believe that each ground of rejection has been overcome by the wording of the new claims.

Specifically, the abbreviations "MT-MMP", "MT-MMP-1", "MT-MMP-2" and "MT-MMP-3" has been omitted from the new claims. Further, the abbreviation "MMP" has been clearly defined in the new claims to mean and to be interchangeable with "matrix metalloproteinase" protein.

With regard to the Examiner's rejection of the phrases "pro MMP-2" and "activation capability of pro MMP-2" (now recited as "pro MMP-2 activating factor"), Applicants believe that the Examiner is mistaken in this regard. Applicants wish to refer the Examiner to the teachings contained on page 29, lines 12-16 and page 75, lines 16-36 of the specification, and in Figure 6A of the drawings. Contained in the noted passages and drawing, each molecular weight of pro MMP-2, its active intermediate and active MMP-2, together with activation of pro MMP-2 is described. Thus, Applicants believe that these phrases are definite under U.S. practice.

In addition, the phrases and terms rejected by the Examiner (i.e. "*which has an activity identical with or substantially identical to naturally-occurring MT-MMP*", "*substantially*", "*protein which has an activity or a primary structural conformation identical with or substantially equivalent to that of MT-MMP-3 or a salt thereof*" and "*(the detection and/or measurement of MT-MMP-3)*") have been omitted from the new claims.

Lastly, the terms "partial peptide" and "anti-serum" have been more particularly defined in the new claims as per the Examiner's request.

Thus, in light of the new claims and comments above, Applicants believe that the rejection of claims 14-22 and 26 under 35 U.S.C. § 112, second paragraph, can no longer be sustained and should be withdrawn.

With regard to the rejections of claims 14-22 and 26 under 35 U.S.C. § 112, first paragraph, as set forth on pages 4-8 of the Official Action, Applicants believe that these rejections has been overcome in view of the new claims.

Applicants have amended the claims to correspond with the subject matter allowed in the parent application (Patent Application Serial Number 09/000,041, filed February 20, 1998, now U.S. Patent 6,191,255). Specifically, the claims have been rewritten to direct to antibodies which specifically bind to a matrix metalloproteinase (MMP) protein or a salt thereof (or a partial peptide of said MMP protein or a salt of said partial peptide) which comprise regions which are highly specific for MT-MMP-3 (i.e. the following peptide fragments of SEQ ID No: 2: (a) Gly^{109} to Arg^{119}, (b) Pro^{171} to Gly^{178}, (c) Thr^{229} to Leu^{242} and (d) Asp^{533} to Val^{607})

For example, in the amino acid sequence of SEQ ID No: 2, the following inserts:

(a) Gly^{109} to Arg^{119} (Insert-1)

(b) Pro^{171} to Gly^{178} (Insert-2)

(d) Asp^{533} to Val^{607} (Insert-3)

are observed in MT-MMP-1 but absent among other members of the MMP family (see page 55 lines 1-30 of the specification).

Further, the inserts:

(a) Gly^{109} to Arg^{119} (Insert-1)

(b) Pro^{171} to Gly^{178} (Insert-2)

are each included in the antigen peptide for the preparation of monoclonal antibodies (see page 58, line 18 to page 59, line 8 of the specification). All the produced antibodies are reactive with MT-MMP-3 exclusively and not with any other MMP member.

The term "matrix metalloproteinase" (i.e., MMP) is supported by the disclosure teaching that the inventive protein, upon which the claimed antibodies specifically bind, has the following structural properties:

(1) signal peptide

(2) propeptide domain

(3) Zn^{+} binding catalytic domain

(4) hinge domain

(5) hemopexin coagulation enzyme-like domain

These structures are recognized to be common to the MMP family (see page 22, lines 12-24, page 54, lines 18-28 of the specification, and Figures 1A to 1E). For the Examiner's review and consideration, Applicants have enclosed a copy of a diagram of the MT-MMP protein (*see FIG. 1b, on page 62 of Nature, vol. 370 (7), pp. 61-65, 1994*).

In addition, the insert:

(d) Asp^{533} to Val^{607} (Insert-3)

has a low 37% homology to that of MT-MMP-1 (see page 55, line 16 of the specification). It is also important to note that the continuous 24-hydrophobic amino acid sequence, Ala^{564} to Phe^{587}, contained in the insert, functions as a transmembrane domain (see page 55, lines 7-9, page 55, lines 24-30, page 73, lines 3-20 and page 74, lines 5-15 of the specification)

Still further, the insert:

(c) Thr^{229} to Leu^{242} (SEQ ID NO: 8)

is an antigen peptide for the preparation of monoclonal antibodies (see page 58, line 18 to page 59, line 8 of the specification) which result in antibodies which react solely with MT-MMP-3 and not with any other MMP member. Also, the claimed protein has a maximum molecular weight of 69kDa as taught by the disclosure on page 55, lines 35-37.

Finally, detailed disclosure for antibody production techniques (see page 32, line 1 to page 38, line 1 of the specification) together with working examples for the preparation of antibodies (see Example 3 of the specification) clearly demonstrate that it would not require undue experimentation to produce the antibodies of the newly added claims.

As a result, from the above comments, it is clear that the teachings of the present specification enables one skilled in the art to practice the claimed invention since the claimed matrix metalloproteinase protein or salt thereof and the antibodies which specifically bind thereto have been disclosed and taught in considerable detail. Further, based on the teachings of the specification, Applicants have clearly demonstrate that they have possession of the claimed antibodies as of the filing date of the present application.

Thus, in view of the Applicants' new claims and above remarks, Applicants believe that the rejections of claims 14-22 and 26 under 35 U.S.C. § 112, first paragraph, cannot be sustained and should be withdrawn.

With regard to the rejection of claims 14-22 and 26 under 35 U.S.C. § 103(a), as being unpatentable over Young et al. or in view of Serafini et al. (The Journal of Nuclear Medicine,

34/3:533-536), this rejection is deemed to be untenable in view of the new claims and is thus respectfully traversed.

To establish a *prima facie* case of obviousness, the cited references either alone or in combination must teach or suggest the invention as a whole and include all the limitations of the claims. Here in this case, none of the cited references teach or suggest the matrix metalloproteinase protein or a salt of said matrix metalloproteinase protein, or a partial peptide of said matrix metalloproteinase protein or a salt of said partial peptide which comprise the limitations of the claims. For example, neither Young et al. or Serafini et al. teach or suggest peptide fragments of SEQ ID No: 2 (i.e. (a) Gly^{109} to Arg^{119}, (b) Pro^{171} to Gly^{178}, (c) Thr^{229} to Leu^{242} and (d) Asp^{533} to Val^{607}) and continuous antigenic amino acid residues of SEQ ID No: 2 which are characteristic of said matrix metalloproteinase protein.

Young et al. merely disclose endogenous plasma membrane-bound MMP-2 in connection with their investigation on the potential association of MMP-2 with ovarian carcinoma plasma membranes and a finding that MMP-2 can bind with the cell surface. In other words, it is clear that the prior art endogenous plasma membrane-bound MMP-2 is a completely different substance and has a completely different amino acid sequence from matrix metalloproteinase protein of the present invention. Also, the plasma membrane-bound MMP-2 of Young et al. does not teach or suggest the partial peptide of the new claims since no fragment of Young et al.'s MMP-2 teach or suggest "continuous antigenic amino acid residues of SEQ ID No: 2 which are characteristic of the matrix metalloproteinase protein" of the present invention.

Thus, since Young et al. fails to teach or suggest the present matrix metalloproteinase protein or partial peptide thereof as set forth in the new claims, the combination of Young et al. and Serafini et al. will also fail to render obvious the presently claimed invention. As a result, for the foregoing reasons, this rejection also cannot be sustained and should be withdrawn.

To further demonstrate the fact that the prior art fails to teach or suggest the antigens (i.e. the matrix metalloproteinase protein or partial peptide thereof) of the present invention, Applicants have provided an alignment and comparison (*see Appendix 3 enclosed herewith*) of the corresponding amino acid residues in (a) sample partial peptides described in the working examples of the specification, (i.e. SEQ ID Nos. 5 to 8), (b) MT1-MMP and (c) MT2-MMP (*see Genbank Accession No. Z48482, Appendix 4 enclosed herewith*).

Applicants wish to note that the above MT2-MMP (Genbank Accession No. Z48482) is based on a reference (*see Will et al. Pub. Med., DDBJ, August 1, 1995; Appendix 5 enclosed herewith*) which was unknown and unavailable at the time of the filing of the priority patent applications (JP 7-200319, filed July 14, 1995 and JP 7-200320, filing date July 14, 1995).

As shown in Appendix 4, the sample partial peptides of the present invention have a low identity with those of other MMP family members including MT1-MMP (*see USP 6,191,255 B1, column 8, lines 23-27 and column 30, lines 58 to 65*). In fact, although the identity between MT1-MMP and MT3-MMP (or MT-MMP3) reaches 68% (*see USP 6,191,255 B1, column 32, lines 63-67*), the sample partial peptides have only 20 to 50% identities with the corresponding amino acid sequence of MT1-MMP and MT2-MMP.

Thus, given such a showing, it is clear that the claimed antigens of the present invention (i.e. claimed matrix metalloproteinase protein and partial peptide thereof, and salts of the matrix metalloproteinase protein and partial peptide) are clearly distinguishable from that which is known in the art.

In view of the foregoing amendments and remarks, it is respectfully submitted that the application is now in condition for allowance. Such actions is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believe that direct contact with the Applicants' attorney will advance the prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

Motoharu SEIKI et al.

By: _____

Lee Cheng
Registration No. 40,949
Attorney for Applicants

LC/gtn
Washington, D.C.
Telephone (202) 721-8200
August 29, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Page 1, the paragraph inserted between lines 1 and 2 of the specification in the Preliminary Amendment dated December 12, 2000 has been amended as follows.

This application is a ~~D~~divisional application of Patent Application Serial ~~n~~Number 09/000,041 filed February 20, 1998, now ~~pending~~allowed as U.S. Patent 6,191,255, issued February 20, 2001, which is a 371 of PCT/JP96/01956 filed July 12, 1996, ~~also~~currently pending.